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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/445,865	02/11/00	BURKE	P ERD100

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EXAMINER	
NICKOL,G	
ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/445,865	Applicant(s) BURKE ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-28 and 34-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-33 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The Election filed March 23, 2001 (Paper No. 8) in response to the Office Action of February 13, 2001 is acknowledged and has been entered. Claims 1-40 are pending in the application and Claims 1-28, 34-39 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 29-33, and 40 are currently under prosecution

Applicant's election with traverse of Group XII (renumbered as Group XIII due to two Group 3's), claims 29-33, 40 in Paper No 8 is acknowledged. The traversal is on the ground(s) that Groups 12, 13, and 14 share the single inventive concept that NQO2 can activate prodrugs in the presence of substrates such as NRH and its analogues. The argument has been considered but is not found persuasive. The inventions of the various groups are distinct for the reasons set forth in Paper No. 7, page 4 according to PCT Rule 13.2.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

The specification is objected to on page 74, line 6 for improper disclosure of nucleotide sequences which fails to comply with the requirements of 37 CFR 1.821 through 1.825. This definition sets forth limits, in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched

sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. (see MPEP 2422).

The specification is further objected to on page 54, line 1 for reciting "Figure 10" because the figures indicate Figure 10A and Figure 10B. Appropriate corrections are required.

Information Disclosure Statement

The IDS filed, May 4, 2000, in Paper No. 6, has been considered, in part, because several references were not submitted. Those references not submitted were not considered.

Claim Rejections - 35 USC § 112

Claims 29-33 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29-33,40 are rejected as vague and indefinite for reciting "substantially" in claim 29. The term "substantially" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 29-30 are rejected as vague for reciting "wherein the cytotoxic drug is CB1954 or an analogue thereof" in Claim 30 . This recitation is confusing because the cytotoxic drug from which claim 30 depends from refers to the product of bioactivation between the prodrug and

NQO2. This rejection can be obviated by amending claim 30 to recite "wherein the prodrug is CB 1954". (For example, see page 39, line 8).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-33 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of treating a human patient with cancer comprising administering a prodrug which is converted to a substantially cytotoxic drug by the action of NQO2 and nicotinamide roboside (reduced) (NRH) or an analogue thereof which can pass reducing equivalents to NQO2.

The claims are not enabled because the specification provides insufficient guidance and or objective evidence that the method would predictably treat a patient with cancer.

The specification teaches several in-vitro assays of potential co-substrates for the reduction of CB1954 (Figures 7, 8a, 8b), in-vitro assays to estimate the uptake of various co-substrates into Chinese hamster lung embryo fibroblasts (Figure 9), and in-vitro cytotoxicity assays using Chinese hamster lung embryo fibroblasts and glioblastoma cells transfected with NQO2 (Figures 11 and 12, respectively and pages 73-76). Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human therapeutic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly

representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Furthermore, there is no objective evidence or guidance regarding administration of the prodrug in vivo. In general, treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice- particularly strains which have tumor suppressor gene knockouts, and problems of clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model

systems are not predictive. Gura further teaches that very few drugs tested in xenografts models have made it to clinical practice and that attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor site (page 1041, 3rd paragraph). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the pharmaceutical composition would function as claimed.

If applicant were able to overcome the 112 1st paragraph enablement rejection above, the following claims would still be rejected.

Claims 29-33, 40 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a human patient with a target cell to be destroyed comprising administering to the patient CB 1954 which is converted to a cytotoxic drug by the action of NQO2 and nicotinamide roboside (reduced) NRH or an analogue thereof which can pass reducing equivalents to NQO2, does not reasonably provide enablement for the method as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(Because of the indefinite nature of the claim language, it is assumed for examination purposes that CB1954 is a prodrug as previously described in the rejection of claims 29-30 under USC 112 2nd paragraph, above.)

The claims are drawn to a method of treating a human patient with a target cell to be destroyed comprising administering to the patient a prodrug which is converted to a cytotoxic drug by the action of NQO2 and nicotinamide roboside (reduced) NRH or an analogue thereof which can pass reducing equivalents to NQO2 (Claim 29); wherein the cytotoxic drug is CB1954 or an analogue thereof (Claim 30).

This includes administering any and all prodrugs and or any and all analogs of CB1954.

However, one cannot extrapolate the teachings of the specification with the scope of the claims because the claims are drawn to the administration of any and all prodrugs including CB1954 and analogs thereof. The specification provides insufficient guidance and or objective evidence that all prodrugs would effectively be converted into cytotoxic drugs by the action of NQO2. Those of skill in the art of enzymology understand that it would be impossible for every known or potentially known prodrug to be an effective substrate for a particular enzyme especially when there are thousands of potential prodrugs which are not substrates for NQO2. Secondly, the specification provides insufficient guidance and or objective evidence of effective analogs of CB1954 that would also effectively be converted into cytotoxic drugs by the action of NQO2. The specification only teaches that analogues of CB1954 are "suitably" defined as molecules which retain the essential structural features of CB1954, i.e. a benzene ring containing an aziridine ring, two NO2 groups and another substituent R but which differ in either the relative orientation of the substituents and/or in the nature of R (page 37, lines 19-28).

Thus, there are literally hundreds of possible analogs of CB1954, and it would be impossible to predict that any or all such analogs would effectively be converted into cytotoxic drugs by the action of NQO2. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure that any and all analogs of CB1954 or any all prodrugs would effectively be converted into a cytotoxic drug for the treatment of a human patient with a target cell to be destroyed. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
April 8, 2001

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